Dexrazoxane Protects Breast Cancer Patients With Diabetes From Chemotherapy-Induced Cardiotoxicity

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Abstract: *Background:* To evaluate the cardioprotective effect of dexrazoxane (DEX) on chemotherapy in patients with breast cancer with concurrent type 2 diabetes mellitus (DM_2). *Methods:* Eighty female patients with breast cancer with DM_2 were randomly assigned to receive chemotherapy only or chemotherapy plus DEX. All patients received 80 mg/m^2 epirubicin and 500 mg/m^2 cyclophosphamide by intravenous infusion every 3 weeks for a total of 6 cycles. The group assigned to receive chemotherapy alone received placebo 30 minutes before epirubicin administration. The group assigned to receive chemotherapy plus DEX received 800 mg/m^2 DEX 30 minutes before epirubicin administration. Cardiac function and hematology before and after 6 cycles of chemotherapy were analyzed. *Results:* There was no difference in baseline systole or diastole function between the 2 DM_2 groups. Patients receiving chemotherapy alone experienced significantly greater reductions in Ea and significantly greater elevations in E/Ea and Tei index in comparison with patients receiving chemotherapy plus DEX. After chemotherapy, superoxide dismutase was significantly reduced, and serum malondialdehyde (MDA) was significantly increased in patients with DM_2. Serum superoxide dismutase levels were comparable between the 2 groups before and after chemotherapy, MDA levels were comparable between the 2 groups before chemotherapy, whereas serum MDA was significantly higher after chemotherapy in the chemotherapy alone group in comparison with the group that received DEX. *Conculsions:* DEX protects against cardiotoxicity induced by chemotherapy in patients with breast cancer with concurrent DM_2.

Key Indexing Terms: Dexrazoxane; Chemotherapy; Cardiotoxicity; Breast cancer; Diabetes. **[Am J Med Sci 2015;349(5):406–412.]**

Since their introduction in the 1960s, the anthracyclines doxorubicin and epirubicin have been effectively applied in the treatment of breast cancer in adjuvant and palliative regimens[1]; however, their use is limited by cumulative dose-related progressive myocardial damage that can lead to chronic heart failure, reduced quality of life and even death.[2] As an increasing number of women survive breast cancer, the impact of cancer treatment on cardiovascular health is becoming more important. The cardiac abnormalities resulting from anthracycline therapy can be persistent, progressive and irreversible. Because early detection and treatment of cardiotoxicity can reduce its clinical effects, it is particularly important that these adverse effects are appropriately managed.[3] Preclinical identification of left ventricular (LV) dysfunction and appropriate clinical intervention can achieve complete recovery of LV function.[4,5]

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The risk of anthracycline cardiotoxicity is dose related,[6] and although, the mechanism of toxicity is yet to be determined likely involves the generation of reactive oxygen species and induction of cardiac myocyte apoptosis.[2] Recent reports have demonstrated that the improvement of screening techniques may facilitate rapid detection of cardiac toxicity, allowing chemotherapeutic doses to be tailored to patient tolerance.[7–10]

Serial noninvasive surveillance for anthracycline cardiotoxicity has previously centered on the echocardiographic assessment of LV systolic function. However, changes in these indices are symptomatic of significant myocardial dysfunction and cannot predict cardiotoxicity before administration of anthracycline therapy. Tissue Doppler's imaging (TDI) allows measurement of the ventricular walls and mitral annulus, facilitating precise evaluation of LV diastolic performance.[8] Anthracycline can affect LV diastolic function and diastolic filling patterns,[11] thus, this technology may enhance evaluation of cardiac function during anthracycline therapy,[7] enabling the timely interruption of anthracycline administration.

Several parameters of TDI velocity analysis have been used to monitor changes after anthracycline chemotherapy.[9,10] Threshold early diastolic peak velocity of mitral annulus (Ea) and the ratio of transmitral early diastolic peak flow velocity (E) and Ea (E/Ea) provide independent and incremental prognostic information in cardiac diseases.[12] The systolic peak velocity of mitral annulus (Sa) is a sensitive marker of mildly impaired LV systolic function,[13] and lower Sa values are associated with increased mortality.[14]

The Tei index is a Doppler's echocardiographic parameter that reflects global LV function, and the TDI-derived Tei index has been demonstrated to correlate with increasing LV diastolic dysfunction,[15] echocardiographic parameters of LV diastolic and systolic function and filling pressures. Moreover, it may enable prediction of the risk for anthracycline-induced cardiomyopathy.[16]

Administration of the cardioprotective agent DEX (Cardioxane, ICRF-187) with anthracycline has been shown to significantly reduce cardiotoxicity in randomized controlled studies.[17,18] DEX is thought to exert cardioprotection through chelation of iron,[19,20] although additional molecular mechanisms may contribute to cardioprotection,[21] DEX can diminish oxidative damage in cardiomyocytes.[22,23] As anthracyclines are most frequently prescribed to patients with advanced/metastatic breast cancer, the bulk of the evidence demonstrating cardioprotection with DEX has been obtained in this group.[17,18] In this population, DEX facilitates the safe administration of anthracyclines without compromising their efficacy.[24]

In addition to the total cumulative dose of anthracycline, several patient-related features including previous irradiation therapy and predisposition to heart disease were found to influence the risk of cardiotoxicity.[25] Several risk factors, such as age, dose, gender and concomitant radiation therapy, have been well characterized,[2,6,25,26] but the relative risks of diabetes and hypertension are not understood. Diabetes mellitus (DM) is an established risk factor for the development of heart failure and has been recognized as a coronary heart disease by the American Heart Association.[27] Numerous studies have

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demonstrated an association between DM_2 and breast cancer; a meta-analysis of 20 studies (5 case-control studies and 15 cohort studies) indicated an increase of approximately 20% in incidence of breast cancer in patients with diabetes.[28] Large-scale prospective studies to comprehensively evaluate the cardiovascular disease (CVD) risk burden associated with modern adjuvant therapy are urgently required.

This study was designed to investigate the efficacy of DEX in mediating cardioprotection against chemotherapy-induced cardiotoxicity in female patients diagnosed with early-stage breast cancer and DM_2. In addition, we evaluated the influence of DEX on serum superoxide dismutase (SOD) and malondialdehyde (MDA) activity.

METHODS

Patient Eligibility

Between October 2012 and October 2013, 89 female patients diagnosed with early stage breast cancer and DM_2, according to current World Health Organization criteria,[29] were recruited at the 4th affiliated hospital of Hebei Medical University. Inclusion criteria: histologically confirmed diagnosis of early breast cancer; candidate for treatment with an epirubicin-based adjuvant chemotherapy regimen according to international standardized protocols; completely resected unilateral breast cancer; blood pressure within the normal range ($<$140/90 mm Hg); echocardiographic left ventricular ejection fraction value $\geq$50%; normal hepatic and renal function (bilirubin $\leq$1.5 mg/dL, creatinine $\leq$2.0 mg/dL); normal sinus rhythm; no concomitant medications, such as angiotensin-converting enzyme inhibitor, B-receptor blocker (B-block), calcium antagonists oxidative stress parameters such as Vc and V_E. Exclusion criteria: acute DM_2 complications; severe chronic DM_2 complications; acute stress reactions, such as external injury, surgery or infection 1 week before blood collection; history of cardiac disease; hypertension; hypo/hyperthyroidism; hemolytic, hepatic and renal diseases; present or history of coronary artery disease, symptoms of congestive heart failure, established structural heart disease such as cardiomyopathy or valvular disease; history of chemotherapy or radiotherapy; ST-segment or T-wave changes specifically for myocardial ischemia, Q waves and incidental left bundle branch block on electrocardiography.

Patients provided written informed consent. The study protocol, amendments and patient informed consent were approved by the Ethics Committee of Human Research of the 4th affiliated hospital of Hebei Medical University (2012MEC012), which has been certificated by FERCAP.

Study Protocol

All patients received 6 cycles of epirubicin-based (epirubicin and cyclophosphamide) adjuvant chemotherapy over 126 days. Patients with DM_2 were randomly assigned to receive chemotherapy alone or chemotherapy plus DEX at a 1:1 ratio using a randomization number table, and patients were blinded to the therapy they received. All patients received 80 mg/m^2 epirubicin plus 500 mg/m^2 cyclophosphamide by intravenous infusion every 3 weeks for a total of 6 cycles. The group assigned to receive chemotherapy plus DEX received 800 mg/m^2 DEX by intravenous infusion, 30 minutes before epirubicin administration. The group assigned to receive chemotherapy alone received intravenous infusion of 0.9% NaCl (Shijiazhuang No.4 Pharmaceutical Co., Ltd. Shijiazhuang, Hebei, China), 30 minutes before epirubicin administration.

Physical examination included measurement of height, weight and blood pressure. A resting 12-lead electrocardiogram was obtained, and total cumulative dose of epirubicin and laboratory findings were recorded. Standard and TDI transthoracic echocardiographic examination was performed. The blood sampling was performed before chemotherapy for the first time and 12 hours after epirubicin dosing for the second time. Then, the blood sample was immediately processed for the assessment of SOD and MDA. All examinations were all performed at baseline and at the end of chemotherapy treatment. Echocardiography and TDI examinations as well as SOD and MDA assessments were performed by physicians blinded to the patients group.

Study Endpoint

Primary study endpoint was systolic/diastolic function, assessed by conventional and TDI ECG. Second study endpoint was levels of SOD and MDA in blood.

Echocardiographic Examination

All echocardiographic evaluations were performed with the patient in the left lateral decubitus position using the IE33 imaging system (Phillips, Andover, MA) equipped with an S5-1 phased-array probe (2 to 5 MHz). Each patient underwent standard conventional echocardiography and TDI examinations at baseline and at the end of chemotherapy. R-wave peak was used as marker of the end of diastole, and the end of T-wave was used as marker of the end of systole. M-mode images of the LV were obtained in the parasternal long-axis view, and the LV end-diastolic and end-systolic diameters were measured just below the mitral valve leaflet tips after alignment of the cursor perpendicular to the LV wall, according to the American Society of Echocardiography guidelines.[30] Echocardiography was performed by the same investigator, blinded to clinical data, and echocardiogram recordings were assessed by 2 cardiologists blinded to the patient's data. The LV end-diastolic and end-systolic volumes were calculated using the biplane modified Simpson's rule in the 4- and 2-chamber apical views, and the echocardiographic left ventricular ejection fraction was derived from these volumes. The pulsed Doppler's sample volume was positioned at the mitral leaflet tips. E, A and E/A ratio were measured by transmitral Doppler's imaging. The TDI program was set to the pulsed-wave Doppler's mode at a frame rate $>$80/s. Filters were set to exclude high-frequency signals, and the Nyquist limit was adjusted to a velocity range of $-$15 to 15 cm/s. All TDI recordings were obtained during normal respiration. The image angle was adjusted to ensure a parallel alignment of the sampling window. Using the apical 4-chamber view, a $<$5 mm sample volume was placed at the lateral corner of the mitral annulus and subsequently at the medial (or septal) corner.[31] The following parameters were measured at both corners and averaged: Sa, Ea and E/Ea were calculated. The Tei index was calculated from TDI images in which the time interval from the end to the onset of the mitral annular velocity pattern during diastole (am) and the duration of the S wave (bm) were measured,[16] at a sweep speed of 75 mm/s. All parameters were measured during 5 cardiac cycles (selected according to image quality) and averaged.

Measurement of SOD and MDA

Blood samples were obtained from venipuncture of the antecubital vein at 8 AM, after overnight fasting, and centrifuged immediately. Serum was stored at $-$80°C. The blood sampling was performed before chemotherapy and 12 hours after epirubicin dosing. Serum SOD and MDA were measured by photometer (Beckman Coulter, Fullerton, CA) using a kit from Nanjing Jiancheng Bioengineering Institute (Nanjing, Jiangsu,

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